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Published in:
European Journal of Organic Chemistry

DOI:
[10.1002/ejoc.201701469](https://doi.org/10.1002/ejoc.201701469)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Final author's version (accepted by publisher, after peer review)

Publication date:
2018

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Collados, J. F., Ortiz, P., Pérez, J. M., Xia, Y., Koenis, M. A. J., Buma, W. J., Nicu, V. P., & Harutyunyan, S. R. (2018). Enantiospecific Brook Rearrangement of Tertiary Benzylic alpha-Hydroxysilanes. *European Journal of Organic Chemistry*, 2018(29), 3900-3903. <https://doi.org/10.1002/ejoc.201701469>

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Enantiospecific Brook Rearrangement of Tertiary Benzylic α -Hydroxysilanes

Juan F. Collados,^[a] Pablo Ortiz,^[a] Juana M. Pérez,^[a] Yiyin Xia,^[b] Mark A. J. Koenis,^[b] Wybren J. Buma,^[b] Valentin P. Nicu,^[b,c] Syuzanna R. Harutyunyan^{*[a]}

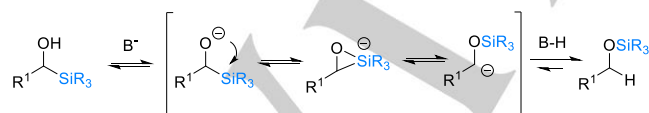
Abstract: The Brook rearrangement of simple, chiral tertiary benzylic α -hydroxysilanes is presented. The rearrangement followed by proton trapping is enantiospecific and proceeds with inversion of configuration at the carbon center. Importantly, the [1,2]-Brook rearrangement can be followed by trapping of methyl or allyl electrophiles even in the protic environment, although with minimal retention of chirality.

Introduction

Since its discovery, the [1,2]-Brook rearrangement, defined as the reversible transformation from α -silyl oxyanions to α -silyloxy carbanions (Scheme 1),^[1] has attracted considerable attention, both regarding the mechanism and its implementation in organic synthesis.^[2] Recently, Marek et al. and our group independently reported the stereoselective [1,2]-Brook rearrangement-trapping sequence of allylic hydroxysilanes.^[3] The presence of either an allyl or alkenyl group in the hydroxysilane is a common feature in enantiospecific variants of the [1,2]-Brook rearrangement because of the enhanced configurational stability of the carbanion after migration of the metal to the beta carbon.^[3,4] Another interesting reaction sequence involving stereoselective Brook rearrangement/acylation sequence was reported by Johnson et al.^[5] Conversely, α -hydroxysilanes lacking configuration stabilizing groups have been less explored in the [1,2]-Brook rearrangement.

Scheme 1. General [1,2]-Brook rearrangement

[1,2] Brook rearrangement

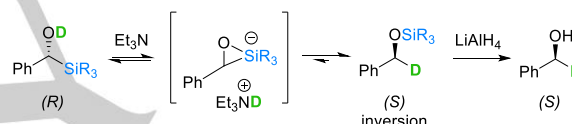


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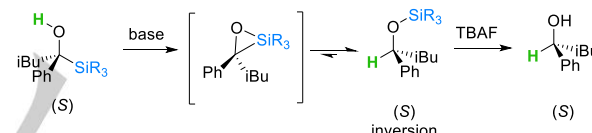
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Following the initial discovery of the Brook rearrangement both Brook and coworkers^[6a] and Mosher and coworkers^[6b] reported examples of the rearrangement of secondary benzylic α -hydroxysilanes including the stereochemistry of the process. Brook et al. used a chiral silicon whereas Mosher et al. used chiral deuterated α -hydroxysilanes, but both reported that the rearrangement proceeded with inversion of configuration at the carbon centre (Scheme 2, a).^[5b] Shortly after, West et al. showed that the reverse rearrangement, the migration of silicon from oxygen to carbon, is also stereospecific and proceeds with inversion of configuration.^[7] Stereospecific Brook rearrangement was also reported for tertiary α -hydroxysilanes with aliphatic six member cyclic structures.^[8] In these examples the

a) Secondary α -hydroxysilanes (Mosher et al.)



b) Tertiary α -hydroxysilanes (this work)



stereospecificity of the rearrangement was rationalized by kinetic equatorial protonation of the anionic intermediate owing to the cyclic structure of the corresponding α -hydroxysilanes.

Scheme 2. a) [1,2]-Brook rearrangement of deuterated secondary benzylic α -hydroxysilanes reported by Mosher.^[6b] b) Enantiospecific [1,2]-Brook rearrangement of tertiary benzylic α -hydroxysilanes.

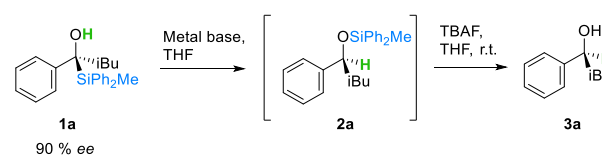
Recently we developed catalytic asymmetric addition of Grignard reagents to acylsilanes, which for the first time allows access to enantioenriched chiral tertiary benzylic α -hydroxysilanes.^[9] Here we report our findings on Brook rearrangements of these tertiary benzylic α -hydroxysilanes and the stereochemistry of the process (Scheme 2, b).

Results and Discussion

We started investigating the reaction of benzyl α -hydroxysilane **1a**^[9] (90 % ee) with a variety of metal bases that could trigger the Brook rearrangement. A mixture of **1a** and the corresponding base (1 equivalent) was stirred overnight in THF at room temperature and then quenched and analyzed by ¹H NMR. Et₂Zn, which initiated the Brook rearrangement for allylic

hydroxysilanes^[3] did not work for the benzylic counterpart and deprotonation with MeMgBr did not trigger the rearrangement either. In both cases, forcing of the reaction conditions by a light warm up resulted in decomposition products. In contrast, in the presence of a lithium base (LiOtBu), Brook rearrangement did take place and the corresponding product **2a** was obtained with full conversion. Alcohol **3a** was then cleanly obtained after desilylation with TBAF (Table 1, entry 1) with an ee of 40%. Subsequently we studied the influence of the different reaction parameters on the stereospecificity of the process (Table 1). The first experiment had been carried out with one equivalent of LiOtBu. However, since it is known that even catalytic amounts of a base can trigger the Brook rearrangement,^[1,2a] we tried to reduce the amount of LiOtBu. With 0.5 equivalents of base the outcome was the same as with 1 equivalent but, interestingly, from that point on, decreasing the amount of base resulted in an increase of the ee of the product. With 20 % of LiOtBu the enantioselectivity rose to 75 % and with 5 % of base the product was obtained with nearly full transfer of chirality (entries 2-4). Only with 1% of LiOtBu no Brook rearrangement took place (entry 5).

Table 1. Conditions screening for the enantiospecific Brook rearrangement.



Entry	Metal base (equiv.)	Temp.(°C)	Conv. (%) ^[a]	ee (%) ^[b]
1	LiOtBu (100%)	r.t.	100	40
2	LiOtBu (50%)	r.t.	100	40
3	LiOtBu (20%)	r.t.	100	75
4	LiOtBu (5%)	r.t.	100	88
5	LiOtBu (1%)	r.t.	0	-
6	LiOtBu (5%)	-78 to r.t.	100	88
7	LiOtBu (5%)	-50	100	73
8	LiOtBu (5%)	0	100	80
9	MeMgBr (5%)	r.t.	0	-
10	Et ₂ Zn (5%)	r.t.	0	-
11	Me ₃ Al (5%)	r.t.	0	-
12	KOtBu (5%)	r.t.	100	80
13	Li Naphthoxide (5%)	r.t.	80	84

Reaction conditions: 0.1 mmol of **1a**, 1 mL of THF and base. Stirred for 3-24 h. Deprotected using TBAF (tetrabutyl ammonium fluoride).^[a] Determined by ¹H NMR spectroscopy. ^[b] Enantiomeric excess was determined by chiral HPLC.

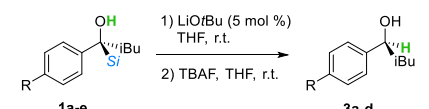
This behavior can be rationalized on the basis of different equilibria controlling the reactions under catalytic or

stoichiometric conditions. It is known that with catalytic amounts of base the equilibrium depends on the relative stabilities of the neutral hydroxysilane and silyl ether, while with excess of base the equilibrium is determined by the relative stabilities of the charged species, namely the alkoxide and the carbanion (Scheme 1).^[2a]

We then studied the effect of the temperature on the reaction. No reaction took place at -78 °C, but adding the base at -78 °C and letting it slowly warm up to room temperature yielded the product in 88 % ee (entry 6). The Brook rearrangement was also observed at -50 °C, yielding the product in slightly lower ee (73 %), and at 0 °C, giving results that approach those at room temperature (entry 8). These results clearly indicate that there is no particular dependence of the enantioselectivity of the process on the temperature, but that, as expected, longer reaction times are required to reach full conversion at low temperature (3h at r.t. vs. overnight at -50 °C). Finally we examined the role of the metal base under catalytic conditions (entries 9-13). In line with the initial experiments described above, no Brook rearrangement took place using MeMgBr or Et₂Zn as a base, while Me₃Al also did not trigger the rearrangement. Interestingly, with KOtBu full conversion to **2a** was observed and lithium naphthoxide triggered the Brook rearrangement too. From these results it can be concluded that only alkali metals trigger the Brook rearrangement. This is further supported by the observation that NaH can start the process as well (not shown in the table). Alkoxides formed from alkali metals are expected to be less stable than those derived from Mg, Zn or Al, which could be the reason for the rearrangement taking place.

With the aim of studying the electronic effects in the carbon and the influence of the silicon centre in the stereospecificity of the rearrangement we conducted further experiments. First we synthesized several structural analogues of the standard hydroxysilane **1a** and subjected them to the Brook rearrangement (Table 2). Products **2b-e** were obtained after overnight reactions. The enantioselectivities of the deprotected products **3b-e** were slightly lower than the original values for the starting silylated alcohols **1b-e**. Both substrates **1b** and **1c**, with electron withdrawing and donating groups, respectively, had the same loss of 12 percentage points of ee (entries 2-3). This indicates that electronics play a minimal role in the transfer of chirality during the rearrangement step. This is corroborated by entry 5, where methoxy, a very strong electron donating group, was used and the same enantioselectivity was obtained after the rearrangement.

Table 2. Influence of the substrate substituents on the Brook rearrangement.



Entry	Substrate, ee (%)	R	Si moiety	Product, ee (%) ^[a]
1	90	H	SiPh ₂ Me	40
2	88	OMe	SiPh ₂ Me	76
3	88	Me	SiPh ₂ Me	76
4	80	OMe	SiPh ₂ Me	68
5	80	Me	SiPh ₂ Me	68

1	1a , 90	H	SiPh ₂ Me	3a , 80-88
2	1b , 85	F	SiPh ₂ Me	3b , 73
3	1c , 92	<i>t</i> Bu	SiPh ₂ Me	3c , 81
4 ^[b]	1c , 92	<i>t</i> Bu	SiPh ₂ Me	3c , 85
5	1d , 24	OMe	SiPh ₂ Me	3d , 24 ^[c]
6	1e , 75	H	SiPhMe ₂	3a , 60

Reaction conditions: 0.1 mmol of **1**, 1 mL of THF, 5 mol % of LiOtBu. Stirred for 3 h to 24 h depending on the substrate. The intermediate silyl ether was deprotected using TBAF (tetrabutyl ammonium fluoride). [a] Enantiomeric excess was determined by chiral HPLC. [b] The reaction was stopped and analysed after 20% conversion. [c] 80% yield in Brook rearrangement after overnight reaction.

Similarly, the substitution at the silicon atom does not seem to affect the stereochemical outcome of the Brook rearrangement either, as the loss of chirality with compound **1e** corresponds to 15% ee, comparable to the other results (entry 6). To investigate if the ee changes as the reaction progresses, an experiment using substrate **1c** was carried out, quenching the reaction after 5 h, with a 20% of conversion to the product **2c**. An increased enantioselectivity of 85% observed in this case (compared to 81 % ee at full conversion, entry 3) might be related to the amount of base with respect to substrate. At conversions higher than 75% the amount of base with respect to the remaining substrate resembles the same situation as in entries 1-4 in Table 1, where the increased amount of base causes a decrease in enantioselectivity. Therefore it is likely that the last 20% of the substrate is converted to the product with lower enantioselectivity, thus leading to an overall decrease in enantioselectivity at full conversion.

Original [1,2] Brook rearrangement of secondary benzylic α -hydroxysilanes has been reported to proceed with inversion of configuration.^[6b] In order to see if this holds true for the tertiary counterparts we determined the absolute configuration of the starting material **1a** and that of the product **3a**. The latter was determined to be *S* by comparison with the reported optical rotation.^[10] Vibrational Circular Dichroism (VCD) was used for determining the absolute configuration of the starting material **1a** (for further details see Supporting Information).^[11] We measured the VCD spectra of both hydroxysilane **1a** and ent-**1a** (Figure 1) and found that the first fitted well with the calculated spectra for the *S* enantiomer (Figure 2). We thus conclude that the Brook rearrangement of tertiary benzylic α -hydroxysilanes proceeds with inversion of configuration.

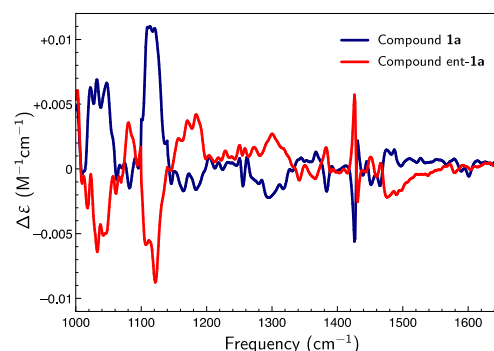


Figure 1. Measured VCD spectra of compounds **1a** and ent-**1a**.

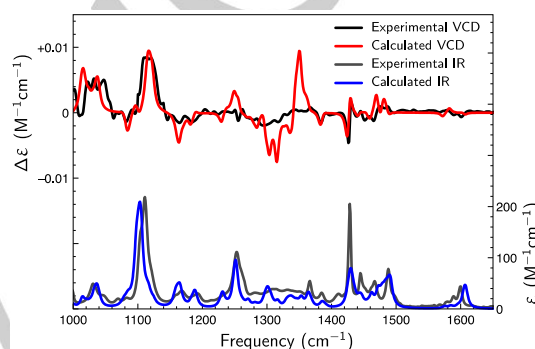
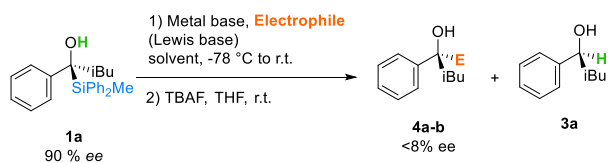


Figure 2. Experimental and calculated IR and VCD spectra of compound **1a**.

The Brook rearrangement, followed by trapping of carbon electrophiles, is a powerful strategy for C-C bond formation.^[2] However, as mentioned in the introduction, the stereoselective variants require allyl systems, configurationally stable allenyl species, or the presence of a coordinating group such as carbamoyl to configurationally stabilize the carbanion.

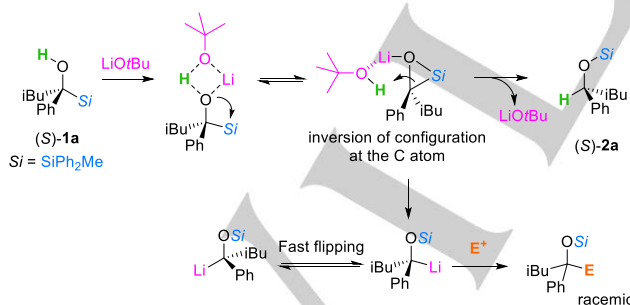
We tested several electrophiles, including acyl chlorides, aldehydes, alkyl halides and Michael acceptors, but only methyl iodide and allyl bromide led to the corresponding trapping products **4**, which were racemic (Scheme 3). Variable amounts of protonated product **3a** were also obtained in these reactions, due to the competition with protonation. When the presence of protons in the media was avoided by using *n*BuLi instead of LiOtBu, full conversion to the trapping products **4a-b** was achieved, but the product was again racemic. This can be rationalized on the basis that carbanions without any stabilizing substituents will racemize very fast. Consequently, we thought of configurationally stabilizing the carbanion using an external Lewis base that can coordinate both with silicon and lithium atoms. DMF, HMPA and TMEDA were tried for this purpose but unfortunately the ee did not surpass 8% (Scheme 3).



Scheme 3. Brook rearrangement/trapping of carbon electrophiles tandem attempts.

Most reports on [1,2]-Brook rearrangement do not propose a mechanism to explain the stereochemical outcome. For secondary benzylic α -hydroxysilanes we distinguish three possible scenarios:^[6b] 1) fast protonation of the carbanion before flipping takes place; 2) transfer of the proton from the solvated base to the carbon in the pentacoordinated intermediate; 3) transfer of the proton from the base coordinated to the oxygen to the carbon in the pentacoordinated intermediate.

Our results seem to suggest the third scenario. We therefore propose a mechanism in which LiOtBu deprotonates the hydroxysilane **1a**, followed by the attack of oxygen to the silicon and formation of the pentacoordinate intermediate. We believe that at this stage the proton is trapped directly from the pentacoordinate silicon intermediate, as it is in the vicinity thanks to the coordination of the $t\text{BuOH}$ to the lithium (Scheme 4). Support for the intramolecular mechanism was gained when the deprotonation/Brook rearrangement was carried out with $n\text{BuLi}$ and the reaction was warmed up before adding the proton source. In this case the corresponding protonated product was formed, but completely racemic. The proposed concerted mechanism would explain the enantiospecificity of the reaction in the case of trapping of protons and the loss of it for external electrophiles. In the latter case the pentacoordinate silicon intermediate would evolve to the chiral carbanion which would quickly racemize and thus the product of the trapping would lose the enantioenrichment (Scheme 4).^[6b]



Scheme 4. Proposed mechanism for the stereospecific protonation of tertiary benzylic α -hydroxysilane **1a**.

Conclusions

In summary, we have explored the Brook rearrangement of simple, chiral tertiary benzylic α -hydroxysilanes. We have demonstrated that the rearrangement followed by proton trapping is enantiospecific and proceeds with inversion of configuration at the carbon analogously to their secondary counterparts. Moreover, we have found that a catalytic amount of base is not only sufficient, but beneficial for the enantiospecificity of the process. Importantly, the [1,2]-Brook rearrangement can be followed by trapping of methyl or allyl electrophiles even in the protic environment, however, in all cases with minimal retention of chirality.

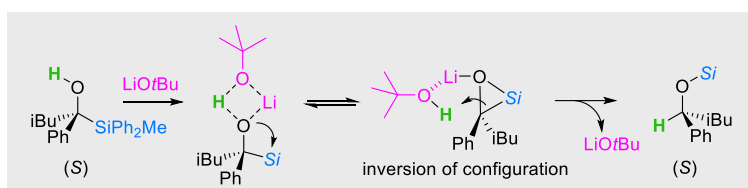
Acknowledgements

Financial support from The Netherlands Organization for Scientific Research (NWO-Vidi and ECHO to S.R.H.) and the Ministry of Education, Culture and Science (Gravity program 024.001.035 to S.R.H.) is acknowledged. J.M.P. thanks to the European Commission for an Intra-European Marie Curie fellowship (grant 746011 – ChirPyr). This research received further support from NWO in the framework of the Fund New Chemical Innovations (NWO Project Nr. 731.014.209).

Keywords: Brook rearrangement • Hydroxysilanes • Enantiospecific • Chirality • Vibrational Circular Dichroism

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COMMUNICATION



Chiral tertiary benzylic α -hydroxysilanes, upon treatment with LiOtBu , undergo Brook Rearrangement, which is enantiospecific and proceeds with inversion of configuration.

Brook rearrangement*

Juan F. Collados, Pablo Ortiz, Juana M. Pérez, Yiyin Xia, Mark A. J. Koenis, Wybren J. Buma, Valentin P. Nicu, Syuzanna R. Harutyunyan*

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